

October 6, 2009

Via EFS-WEB

Commissioner for Patents  
U.S. Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450

RE: U.S. Patent Application No. 10/561,826  
Title: Neuronal Differentiation of Stem Cells  
Inventors: Catherine M. Verfaillie et al.  
Attorney Docket: 890003-2006.1

Sir:

The following document is forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

- Substance of Interview.

Applicants do not believe that any fees are due with filing. In the event that fees are incurred, however, the U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency to our Deposit Account No. 20-0809.

Respectfully submitted,



Anne Brown  
Registration No. 36,463

Enclosure

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of

Applicant(s) : Catherine M. Verfaillie et al.  
Application No. : 10/561,826  
Filed : October 17, 2006  
Title : Neuronal Differentiation of Stem Cells  
Examiner : Chang Yu Wang  
Art Unit : 1649  
Attorney Docket : 890003-2006.1

**SUBSTANCE OF INTERVIEW**

Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

Sir:

The following Substance of Interview for the above-identified patent application is submitted in compliance with MPEP § 713.04.

A telephonic interview was held on September 8, 2009, regarding the above-identified matter. In attendance were Examiner Chang-Wu Wang, Supervisory Examiner Christine Saoud, and Applicants' attorney, Anne Brown. Applicants' attorney provided a handout to Examiner Wang on September 4. This handout was used to discuss the rejection under 35 U.S.C. § 103 and § 112 (new matter).

§ 103: The Cited Art vs. Claim 4

The second page of the handout showed previous claims 1 and 4. The invention is generally directed to a method for differentiating a stem cell into a neural cell by culturing the stem cell sequentially with four growth factors: (1) basic fibroblast growth factor (bFGF), (2) a combination of fibroblast growth factor 8 (FGF8) and sonic hedgehog (SHH), and (3) brain-derived neurotrophic factors (BDNF). These are all mandatory factors and are administered sequentially to the stem cell.

Claim 4, which is the claim at issue, requires that each step is performed for at least seven days. That means seven days with bFGF, seven more days with FGF8 and SHH, and seven more days with BDNF.

Page 7 of the handout showed the **Examiner's rationale for rejecting claim 4**. It is essentially as follows: the prior art does not explicitly teach seven days for each step. However, **in the prior art, the whole culture procedure takes more than a month, "which is within the limitations of instant claim 4."** Applicants' attorney explained that the month-long prior art procedure is not within the limitations of claim 4 because **three weeks of that month do not involve exposure to the four claimed factors**.

This was evidenced on pages 3-6 of the handout. Page 3 shows that the cited art teaches five distinct procedures for generating five different types of CNS cells. For the gaba-ergic neuron, the procedure specifically excludes SHH and FGF8. Also, BDNF is not used. So the four growth factors are not used in this procedure. For serotonergic neurons, astrocytes, and oligodendrocytes, BDNF is not used. So only three of the four growth factors are used.

For dopaminergic neurons, however, bFGF, SHH, and FGF8 are used. BDNF is **suggested as optional (out of 21 possible growth factors)**. So, Applicants' attorney focused on dopaminergic neurons because that is the only procedure that even suggests using the four factors.

Page 4 of the handout (top arrows) shows a timeline for making dopaminergic neurons. There are five stages for differentiating the embryonic stem cell. The first expands the cells; **none of the factors are used in this stage**. The second generates embryoid bodies; **none of the factors are used at this stage**. The third generates a neural-committed cell from the embryoid body; **none of the factors are used at this stage**. This covers 3-5 days, 3-6 days, and 9-16 days, respectively. **There is only one stage in this procedure (Stage IV) when all the growth factors are used**. That is shown in the box on page 4. The factors are all administered together and cultured for **seven days only**. The administration of these factors creates an expanded neural-committed cell. Differentiation (Stage V) is accomplished by **withdrawing one of the factors** and culturing for five more days.

With claim 4 (in the box below the prior art timeline), the procedure with the four factors is very different. bFGF is exposed to the cells for seven days. Only after that are FGF8 and SHH added for seven more days. And only after that is BDNF added for seven more days. This is a 21-day sequential procedure as opposed to a seven-day simultaneous procedure that is done in the prior art.

On page 6 of the handout, Applicants' attorney showed a schematic summary of the procedure in the cited art compared to the procedure in claim 4. The round circles represent petri dishes. In the art procedure, bFGF, SHH, FGF8, and BDNF (which is optional) are incubated all together with the cells for seven days total. The claims require what is underneath the line. This is a 21-day sequential procedure with the four growth factors.

#### Examiner's Rationale

Returning to the stated rationale, the Examiner states each step in each stage requires 6-9 days and the whole procedure takes more than a month, "which is within the limitations of the claim." But, as shown in the handout and discussed above, over the space of that month, **only seven days involve exposure to the four factors**. So it is irrelevant that the whole procedure takes more than a month because the cells are exposed to the claimed factors for only seven days of that month. Therefore, the art is not within the limitations of claim 4.

#### Examiner's Comments in the Interview

After Applicants' attorney presented the diagrams, Examiner Wang commented that, in the prior art method, the cell is incubated with each of the factors for seven days. She pointed out that in the claimed procedure, although the factors are added sequentially, the cells are also exposed to each of the factors for seven days. The implication was that the same results would have been produced by exposing the cell to each factor for seven days whether simultaneously or sequentially. Applicants' attorney pointed out that the purpose of the diagrams and discussion was to respond specifically to the Examiner's stated point of argument about the prior art procedure taking a month. In the rejection, the Examiner relied on that fact. So, that reliance was the subject of the interview.

However, since the Examiner commented, Applicants' attorney explained that it was not reasonably predictable that sequential exposure would produce the same result as simultaneous exposure. In fact, this is the very point that Dr. Verfaillie addressed in the (unconsidered) Declaration, i.e., that one could not reasonably expect the same result with sequential exposure to the factors as one would expect with simultaneous exposure to the factors. The Declaration is unequivocal on this, so Applicants' attorney had not found it necessary to discuss it in the interview.

#### New Matter

With respect to the new matter rejection, claims 7 and 8 were rejected on the grounds that the phrase "cells that are not embryonic stem cells, embryonic germ cells, or germ cells and can differentiate into at least one cell type of each of the endodermal, ectodermal, and mesodermal embryonic lineages" is not disclosed in the specification and, thus, is new matter. During prosecution, Applicants had presented an Appendix showing that this language was incorporated by reference from the parent PCT application (PCT/US00/21387). The handout contained the face page and text of that parent application stating that the cells of the invention are non-embryonic stem cells that can give rise to cell lineages of all three germ

layers. It also specifically incorporates by reference the parent application, which has already issued into a patent and an allowed application (11/238,234).

Page 14 of the handout shows the language of allowed claims in U.S. 10/048,757, a continuation of the parent PCT application. The claims contain the rejected phrase.

Applicants' attorney went through the materials presented during examination. Primary Examiner Saoud indicated that she would discuss with the Specialist whether incorporation by reference would be sufficient to overcome the new matter rejection.

Applicants do not believe that any fees are due with this filing. However, in the event that fees are due, the Commissioner is hereby authorized to charge any additional fees required or to credit any overpayment to Deposit Account 20-0809. The applicant(s) hereby authorizes the Commissioner under 37 C.F.R. §1.136(a)(3) to treat any paper that is filed in this application which requires an extension of time as incorporating a request for such an extension.

Respectfully submitted,



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October 6, 2009

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